UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF SOLID LIPID NANOPARTICLES FOR ORAL DELIVERY OF ACYCLOVIR AND EVALUATION OF ITS PHARMACOKINETICS PROFILE

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By

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DEVELOPMENT OF SOLID LIPID NANOPARTICLES FOR ORAL DELIVERY OF ACYCLOVIR AND EVALUATION OF ITS PHARMACOKINETICS PROFILE

By

HANIZA BINTI HASSAN

September 2018

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Herpes simplex virus (HSV) type 1 and type 2 infections have become a significant global health and economic burden. These infections are life-long and symptoms of HSV infection are usually painful episodes of blisters and ulceration of skin around the infected area. Acyclovir, an antiviral drug, is prescribed to the patients in order to treat the infectious diseases. However, there are drawbacks associated with the use of acyclovir such as unwarranted high-doses-related adverse effects. Higher doses of acyclovir are given to patient in order to achieve its desired therapeutic effect, since acyclovir is known to have poor oral bioavailability.

In order to improve the efficacy and oral bioavailability of acyclovir, solid lipid nanoparticles were developed as acyclovir carriers due to the advantages and its unique properties over the other colloidal drug delivery system. To date, this study is the first to design and optimize two types of solid lipid nanoparticles dispersions developed from glyceryl behanate (Compritol 888 ATO) and glyceryl palmitostearate (Biogapress Vegetal 297 ATO) using response surface methodology to encapsulate acyclovir for its oral administration. The characteristics of the solid lipid nanoparticles loaded with acyclovir and their *in vivo* pharmacokinetic parameters were also evaluated.

Response surface methodology was used to optimize the main composition; solid lipid and surfactant, Tween 80 and their influence on three main properties of solid lipid nanoparticles, namely particle size, polydispersity index and zeta potential were investigated. The optimization process of the main compositions was carried out in order to achieve optimum solid lipid nanoparticles formulations. The data analyses showed that variation in all responses could be described as quadratic

function of the composition of solid lipid nanoparticles dispersions and well fitted into a second-order polynomial model.

In continuation of the optimization process, the optimized formulations, as suggested by response surface methodology were employed to fabricate acyclovir-loaded solid lipid nanoparticles dispersions. The solid lipid nanoparticles from Compritol 888 ATO with particle size of 108 nm, zeta potential of -33 mV and polydispersity index of 0.22 were produced. As for Biogapress Vegetal 297 ATO, the particle size of 123 nm, zeta potential of -27 mV and polydispersity index of 0.22 were successfully fabricated. The entrapment efficiency for both formulations showed relatively good acyclovir encapsulation, between 80-90%. All formulations were stable when stored at refrigerated temperature for three months. Data from the *in vitro* drug release study revealed that both acyclovir-loaded solid lipid nanoparticles dispersions had prolonged acyclovir release in simulated intestinal fluid for up to 24 hours.

The current study also provided *in vivo* oral bioavailability evidence where acyclovir-loaded solid lipid nanoparticles dispersions possessed superior oral bioavailability as compared to the commercial acyclovir suspension when given to rats. Significant increment of acyclovir concentration in rat's plasma was seen throughout the 24-hour bioavailability study suggesting the encapsulation of acyclovir into solid lipid nanoparticles allowed a controlled release of acyclovir following its oral uptake. This study exhibited the feasibility of solid lipid nanoparticles dispersions as oral delivery vehicle for acyclovir whereby both acyclovir-loaded Compritol 888 ATO SLNs and Biogapres Vegetal 297 ATO SLNs investigated in this study have proven to enhance the absorption and oral bioavailability of acyclovir. This will therefore represent a new promising therapeutic concept of nanoparticulate delivery system for acyclovir.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PEMBANGUNAN NANOPARTIKEL LIPID PEPEJAL SEBAGAI PENYAMPAI ASIKLOVIR SECARA ORAL DAN PENILAIAN PROFIL FARMAKOKINETIKNYA

Oleh

HANIZA BINTI HASSAN

September 2018

Pengerusi : Prof. Madya Rusliza Binti Basir, PhD
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Dewasa ini, jangkitan *Herpes simplex* virus jenis 1 dan jenis 2 telah menjadi bebanan kesihatan dan ekonomi penduduk secara global. Jangkitan virus ini adalah seumur hidup dan antara gejala yang biasa dijumpai adalah lepuhan dan ulser kulit yang menyakitkan di sekitar kawasan yang dijangkiti oleh virus. Asiklovir, sejenis ubat antiviral diberikan kepada pesakit untuk merawat penyakit berjangkit ini. Walau bagaimanapun, penggunaan asiklovir boleh mengakibatkan kesan sampingan buruk lanjutan pengambilannya secara oral dalam dos yang tinggi. Keperluan kepada dos tinggi ini yang diberikan kepada pesakit bagi mencapai kesan terapeutik yang diperlukan disebabkan beberapa faktor, termasuk biokeperolehan asiklovir yang diberikan secara oral sangat rendah.

Dalam kajian ini, nanopartikel dari sumber lipid pepejal telah direka dan dibangunkan untuk meningkatkan keberkesanan dan biokeperolehan asiklovir secara oral. Sebagai sistem penyampaian ubat, nanopartikel lipid pepejal mempunyai banyak kelebihan dan bersifat unik berbanding penyampaian ubat koloid yang lain. Proses pembangunan dan pengoptimuman dua jenis nanopartikel lipid pepejal yang dibangunkan dari glyceryl behanate (Compritol 888 ATO) dan glyceryl palmitostearate (Biogapress Vegetal 297 ATO) telah dikaji. Ciri-ciri nanopartikel lipid pepejal yang baharu dibentuk yang memuatkan asiklovir juga telah dinilai.

Kaedah tindak balas permukaan (RSM) telah digunakan dalam proses pengoptimuman komposisi utama bagi kedua-dua jenis nanopartikel lipid pepejal dan dijalankan untuk mendapatkan formulasi nanopartikel lipid pepejal yang optimum. Analisis tindakbalas permukaan menunjukkan bahawa variasi dalam

ketiga-tiga tindakbalas boleh digambarkan sebagai bentuk fungsi kuadratik bagi semua komposisi utama dalam penyediaan nanopartikel lipid pepejal dan data eksperimen menepati model polinomial peringkat kedua.

Kesinambungan kepada proses pengoptimuman formulasi nanopartikel, formulasi optimum yang dicadangkan oleh kaedah tindak balas permukaan telah digunakan dalam pembuatan nanopartikel lipid pepejal yang mengandungi asiklovir. Asiklovir yang dimuatkan di dalam nanopartikel lipid pepejal dari Compritol 888 ATO dengan saiz zarah 108 nm, potensi zeta -33 mV dan indeks polisebaran 0.22 telah berjaya dihasilkan. Nanopartikel yang diperbuat dari Biogapress Vegetal 297 ATO dengan saiz zarah 123 nm, potensi zeta -27 mV dan indeks polisebaran 0.22 juga telah berjaya direka. Kecekapan pemerangkapan untuk kedua-dua formulasi nanopartikel lipid pepejal menunjukkan pengkapsulan asiklovir yang agak baik, di antara 80-90%. Kesemua formulasi yang optimum dilaporkan stabil apabila disimpan pada suhu sejuk untuk jangkamasa tiga bulan. Data dari kajian profil pelepasan ubat secara '*in vitro'* menunjukkan bahawa kedua-dua jenis nanopartikel lipid pepejal yang memuatkan asiklovir telah dapat memanjangkan tempoh pelepasan asiklovir dari sistem nanopartikel ke dalam simulasi cecair usus sehingga tempoh 24 jam.

Kajian *in vivo* semasa juga telah membuktikan bahawa biokeperolehan oral asiklovir yang dimuatkan di dalam nanopartikel lipid pepejal adalah lebih baik berbanding dengan suspensi asiklovir yang dipasarkan secara komersil, apabila diberikan kepada tikus. Peningkatan ketara ke atas kepekatan asiklovir di dalam plasma tikus telah dapat diperhatikan sepanjang kajian biokeperolehan yang berlangsung selama 24 jam, yang menandakan bahawa pengkapsulan asiklovir ke dalam nanopartikel lipid pepejal telah membolehkan pelepasan asiklovir secara terkawal setelah pengambilannya secara oral. Kajian ini juga telah mendedahkan kemungkinan bahawa nanopartikel lipid pepejal yang dibangunkan adalah bersesuaian untuk dijadikan sebagai medium atau alat penghantaran asiklovir secara oral. Oleh yang demikian, dapatan dari kajian ini akan menjadi contoh konsep terapeutik baharu yang memberangsangkan di dalam sistem nanopartikel bertujuan untuk penyampaian ubat.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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ABC	ATP-binding cassette
AFM	atomic force microscopy
AKI	acute kidney injury
ANOVA	analysis of variance
ATN	acute tubular necrosis
AUC	area under the curve
BUN	blood urea nitrogen
C_{max}	maximum concentration
$C_4H_8O_6U$	uranyl acetate
CCD	Central Composite Design
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
DoE	design of experiment
DLS	dynamic light scattering
DSC	differential scanning calorimetry
EE	entrapment efficiency
ED_{50}	median effective dose
FDA	Food and Drug Administration
GIT	gastrointestinal tract
GRAS	generally recognize as safe
H&E	hematoxylin and eosin
HCl	hydrochloric acid
$HClO_4$	perchloric acid
HSV	*Herpes simplex* virus
HSV 1	*Herpes simplex* virus type 1
HSV 2	*Herpes simplex* virus type 2
i.v	intravenous
K_e	elimination constant
KH_2PO_4	potassium dihydrogen phosphate
LAT	latency-associated transcripts
MRI	magnetic resonance imaging
NLC	nanostructured lipid carrier
OVAT	One-Variable-at-a-Time
PBS	phosphate buffered saline
PdI	polydispersity index
RI	recrystallization index
RSM	Response Surface Methodology
SEM	scanning electron microscopy
SLNs	solid lipid nanoparticles
SPE	solid phase extraction
STI	sexually transmitted infection
$T_{1/2}$	elimination half-life
T_{max}	time to reach maximum concentration
TEM	transmission electron microscopy
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

Herpes simplex virus (HSV) infections have caused global health and financial burden (Du et al., 2013). The current treatment option of HSV infections is prescription of an antiviral drug, precisely acyclovir (Elion, 1983; Elion, 1993). However, administration of high doses of acyclovir is required in order to achieve the desired therapeutic effect due to its main pharmacokinetic limitation that is, low oral bioavailability (Kubbinga et al., 2015; Raborn et al., 1987). Also, the current dosage regimen is not patient-compliant, as patients would experience unwarranted adverse effects due to high doses of acyclovir administration. Therefore, the development of a better therapeutic oral delivery system is an interesting area to explore in order to overcome the current pharmacokinetic limitation of acyclovir.

Over the years, the use of nanoparticles in improving drug delivery has grown rapidly. There is an increase expectation that application of nanoparticles in medicine will bring substantial advantages to the diagnosis and treatment of diseases due to their distinctive properties. The relevance of nanotechnology in drug design and drug discovery has led to an exciting new world of nanomedicine - an area to be explored and exploited for future benefits.

1.2 Problem Statements

Fundamentally, acyclovir is active against most of the species in herpes virus family. Acyclovir is actively being absorbed in the upper gastrointestinal tract (GIT) particularly the duodenum as well as jejunum. However, the absorption and oral bioavailability of acyclovir are very low, in the range between 15-30%. Approximately, 70-80 % of the oral dose is not absorbed and excreted via faeces. Also, the terminal half-life of acyclovir is pretty short, which is about 2.5 to 3 hours following drug administration (Smith et al., 2010; Wald et al., 1994).

Due to these unfavourable characteristics, patients are required to take frequent and high doses of acyclovir (200 mg, five times daily, up to ten consecutive days) to achieve its therapeutic efficacy. However, the high doses of acyclovir have shown to result in side effects, which include headache, vomiting, nausea and worst, renal failure (Fleischer & Johnson, 2010; Lu et al., 2014). Therefore, acyclovir is in need of a suitable drug carrier that can be easily loaded with and could improve its current pharmacokinetic drawbacks, especially with regards to administering it at a

less frequent and/or lower dose yet obtaining the desired pharmacological effect. Solid lipid nanoparticles (SLNs) with their potential to be drug carriers have been proposed as good candidates to fulfil this goal by improving the absorption and oral bioavailability of the proposed drug.

Previously, encapsulation of acyclovir in emulsion was a success. However, emulsion was not very stable during shelf storage, where drug leakage was observed and reported (Ghosh et al., 2006). Encapsulation of acyclovir into SLNs may help to overcome the stability issues of this antiviral drug. Only a few studies have been conducted thus far to explore and observe the potential of solid lipid as a carrier for delivery of acyclovir. A drug delivery study showed that solid lipid nanocarrier for the ocular administration of acyclovir has the ability to improve the drug penetration through the corneal membrane (Seyfoddin & Al-Kassas, 2013). Therefore, this will enhance the ocular bioavailability and absorption of acyclovir compared to the naked drug. Apart from that, solid lipid nanocarrier was reported to have a good drug loading capacity and exhibited sustained/controlled-drug delivery characteristic such that longer retention time of acyclovir in the body was observed (Seyfoddin et al., 2015).

1.3 Significance of Study

The practical use of SLNs as a drug carrier for oral drug delivery of acyclovir has not been fully explored. Recently, only few studies have been conducted to develop and evaluate the role and characteristic of lipid nanoparticles as a drug carrier for delivery of acyclovir (Cortesi et al., 2011; Seyfoddin & Al-Kassas, 2013). To date, there was no published study on the SLNs as a potential drug carrier for oral delivery of acyclovir despite of the urgent call to improve the absorption and oral bioavailability of this antiviral agent for the treatment of HSV infection. Investigating the potential role and characteristic of SLNs loaded with acyclovir to improve the oral bioavailability and absorption of acyclovir to combat HSV infection is, therefore, a novel idea that needs to be explored. If the hypothesis that suggests SLNs loaded with acyclovir has the potential to enhance the oral bioavailability of acyclovir is proven, then this will be a breakthrough in antiviral drug research. It will lead to the development of a new alternative oral drug delivery system for acyclovir as well as other antiviral drugs.

1.4 Scope of Study

In this study, two SLNs dispersions loaded with acyclovir for oral administration were designed. Response surface methodology (RSM) was utilized to optimize the SLNs formulations developed using two types of plant-based solid lipid; glyceryl palmitosterate (Biogapress Vegetal 297 ATO) and glyceryl behanate (Compritol 888 ATO). The solid lipid nanoparticles were characterized with respect to the particle size, polydispersity index, zeta potential, pH, viscosity, morphology

analysis, encapsulation efficiency, physical stability and *in vitro* drug release kinetic. The carrier system was evaluated for its *in vivo* pharmacokinetic parameters, to proof the study hypothesis.

1.5 Hypothesis

It is hypothesized that acyclovir-loaded Compritol 888 ATO SLNs and Biogapress Vegetal 297 ATO SLNs will enhance the oral bioavailability and absorption of acyclovir when administered in an *in vivo* model.

1.6 Research Objectives

1.6.1 General Objective

To characterize the properties and evaluate the *in vivo* pharmacokinetics of acyclovir-loaded Compritol 888 ATO and Biogapress Vegetal 297 ATO SLNs dispersions.

1.6.2 Specific Objectives

1. To prepare two SLNs carrier system, Compritol 888 ATO SLNs and Biogapress Vegetal 297 ATO SLNs for acyclovir using combination of hot homogenisation and ultrasonication technique and evaluate the influence of solid lipid and surfactant compositions using response surface methodology on the quality of the SLNs (particle size, polydispersity index and zeta potential) for the optimization process (Chapter 4).

2. To characterize the acyclovir-loaded Compritol 888 ATO SLNs and acyclovir-loaded Biogapress Vegetal 297 ATO SLNs (i.e size, zeta potential and morphology) and evaluate its *in vitro* drug release kinetic (Chapter 5).

3. To evaluate the *in vivo* pharmacokinetics profile of acyclovir following oral administration of acyclovir-loaded Compritol 888 ATO SLNs and acyclovir-loaded Biogapress Vegetal 297 ATO SLNs (Chapter 6).

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BIODATA OF STUDENT

Haniza Hassan was born on 4th of November 1985 in Batu Pahat, Johor. She graduated in 2006 with a Bachelor of Science (Biochemistry and Pharmacology) at the University of Adelaide, Australia. In 2007, she was conferred with a second degree, Bachelor of Health Science (Hons) majoring in Pharmacology from the same institution. Haniza worked on a project entitled 'Impact of nanoparticles on hepatic handling of drugs' and she obtained her Master of Science (Pharmacy) from the University of South Australia in 2012. As her interests in nanotechnology arise, her doctoral project focuses on the development of solid lipid nanoparticles for oral delivery of drugs. Throughout her PhD journey, she has attended national conference and participated in competitions. Haniza is currently working with University Putra Malaysia and with her research experiences, she hopes that she can expend her networking and explore more knowledge.

LIST OF PUBLICATIONS

Haniza Hassan, Siti Khadijah Adam, Fauziah Othman, Ahmad Fuad Shamsuddin, Rusliza Basir (2016). Antiviral Nanodelivery Systems: Current Trends in Acyclovir Administration. *Journal of Nanomaterials*, 2016, 8 pages. doi: 10.1155/2016/4591634. (Published)

Haniza Hassan, Siti Khadijah Adam, Ekram Alias**,** Aishah Saad Abdul Rahim, Ahmad Fuad Shamsuddin, Rusliza Basir (2018). Development and Optimization of Solid Lipid Nanoparticles for Oral Delivery of Acyclovir by Response Surface Method. (Under review)

List of Oral/Poster Presentations

Haniza Hassan, Siti Khadijah Adam, Fauziah Othman, Aishah Saad Abdul Rahim, Ahmad Fuad Shamsuddin, Rusliza Basir. (2016) Optimization of Solid Lipid Nanoparticles Formulation for Oral Delivery of Acyclovir. *30th Scientific Meeting of Malaysian Society of Pharmacology and Physiology (MSPP)*, 2016 (Oral)

Haniza Hassan, Siti Khadijah Adam, Fauziah Othman, Ahmad Fuad Shamsuddin, Rusliza Basir. (2016) Short-term Stability Study of Acyclovir-loaded Solid Lipid Nanoparticles. *30th Scientific Meeting of Malaysian Society of Pharmacology and Physiology (MSPP)*, 2016 (Poster)

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